UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,430	03/09/2005	Jeffery A Bibbs	DIAKR.007NP	5428

20995 7590 07/22/2010

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
BETTON, TIMOTHY E	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
07/22/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
efiling@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/527,430	BIBBS, JEFFERY A	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *7-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Remarks filed on 5 May 2010 have been acknowledged and duly made of record.

Response to Arguments

The rejection under Nonstatutory Double Patenting is hereby withdrawn in consideration of applicants' response in order to remedy the issues for which the said rejection under Nonstatutory Double Patenting was employed. The terminal disclaimer as filed on 22 May 2010 are hereby acknowledged and duly made of record.

The rejection under 35 USC section 103(a) over Pullela is also hereby withdrawn in consideration of applicants' disclosure on page 15 in first 2 full paragraphs of current set of remarks as filed on 5 May 2010 which discloses:

> Applicants need not address the Examiner's substantive arguments. Pullela is disqualified as prior art under 35 U.S.C. §103(c) because the subject matter of Pullela and the claimed invention were subject to a joint research agreement at the time the invention was made. MPEP § 706.02(1)(2). Disqualification of a reference under 35 U.S.C. §103(c) as amended by the CREATE Act applies to a reference under 35 U.S.C. §102(e), (f), or (g) and which is being relied upon in a rejection under 35 U.S.C. §103. *Id.* Therefore, Pullela, which was granted on an application filed before the instant claimed invention, is a 102(e) reference that can be disqualified under 35 U.S.C. § 103(c).
>
> In order to disqualify a reference under 35 U.S.C. §103(c) as amended by the CREATE Act, an applicant must amend the specification to disclose the names of the parties to the joint research agreement in accordance with 37 C.F.R. § 1.71(g) and a statement complying with 37 C.F.R. § 1.104(c)(4). As noted above, the specification has been amended to state the names of the parties to the joint research agreement in compliance with 37 C.F.R. § 1.71(g). A statement complying with 37 C.F.R. § 1.104(c)(4) is separately submitted herewith. As Applicants have complied with the requirements to disqualify Pullela under 35 U.S.C. § 103(c), Applicants request withdrawal of the rejection of Claims 1, 2, 4, and 5 under 35 U.S.C. §103(a) over Pullela.

In full consideration of the foregoing, the said rejection under 35 USC section 103(a) over Pullela et al. is hereby withdrawn.

The rejection under 35 USC section 103(a) over Kumar, Kobrin and Li is averred by applicants due to said rejection allegedly being factually incorrect individually and/or in combination in order to establish obviousness over the claimed invention.

Applicant's arguments, see pages 15-20, filed 5 May 2010, with respect to the primary reference Kumar et al. explicitly teaching that:

> Kumar discloses that there are significant differences between L-type (e.g. nifedipine) and T-type (e.g. PPK-5) calcium channel blockers and that the two different types of blockers do not have the same mechanism of action, affinity for the same channel, or activity. Additionally, a person of ordinary skill in the art cannot generalize L-type and T-type blockers with regard to the claimed invention because Kumar (1) discloses that nifedipine and PPK-5 are pharmacologically completely different and (2) does not disclose any *in vivo* treatment, much less a time course. As such, Kumar itself provides evidence of non-obviousness.

These specific remarks disclosed on page 16 in the second paragraph at lines 6-13 have been fully considered and are persuasive. The rejection under 35 U.S.C. §103(a) based on Kumar, Kobrin, and Li of 5 May 2010 has been withdrawn.

Status of the Claims

Claims 1, 2,4,5, and 7-11 are currently pending further prosecution on the merits. Claims 7-11 are withdrawn from further consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting calcium T-channel activity with a T-channel antagonist

of Formula I, does not reasonably provide enablement for a method of inhibiting calcium T-channel activity with a prodrug of a T-channel antagonist of Formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In re Wands, set forth the following eight factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph:

1) the quantity of experimentation necessary
2) the amount of direction or guidance provided
3) the presence or absence of working examples
4) the nature of the invention
5) the state of the art
6) the relative skill of those in the art
7) the predictability of the art and
8) the breadth of the claim

The breadth of the claims is broadly drawn to a method for inhibiting calcium T-channel activity with a selective T-channel antagonist.

The state of the art is relates to certain dihydropyrimidine, dihydropyrimidone, dihydropyrimidinethione, and dihydropyridine compounds that can modulate the activity of calcium channels. These compounds can also be used for the treatment of diseases, such as cardiovascular disease, that are associated with calcium channels.

The nature of the invention is drawn to a method of selectively inhibiting calcium T-channel activity.

Paragraph 22 describes the term “prodrug” as the following:

A "prodrug" refers to an agent that is converted into the parent drug in vivo. Prodrugs are often useful because, in some situations, they may be" easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxyl acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

However, the direction and guidance required in order to elucidate this particular aspect of Formula I in view of claim 4 is absent in the Examples which follow. The lacks representative data clearly showing the limitation of said claim 4. Examples beginning on pages 40 and culminating at or around page 71 disclose various aspects which mention nothing with regard to testing the selectivity of a prodrug of Formula I for inhibiting T-channel activity.

Predictability would be high due to the lack of a representative model or data clearly delineating the methods of administration of a prodrug of Formula I in comparison to the title compound of Formula I.

Therefore, the quantity of experimentation necessary could not be readily determined based upon the lack of factual evidence drawn to a method of inhibiting T-channel activity with a prodrug of Formula I.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, and 7-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods as described in the Examples of pages 40-71, does not reasonably provide enablement for a method of inhibiting calcium T-channel activity with the title T-channel antagonist of Formula I and the derivatives of claim 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In re Wands, set forth the following eight factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph:

1) the quantity of experimentation necessary
2) the amount of direction or guidance provided
3) the presence or absence of working examples
4) the nature of the invention
5) the state of the art
6) the relative skill of those in the art
7) the predictability of the art and
8) the breadth of the claim

The breadth of the claims is broadly drawn to a method for inhibiting calcium T-channel activity with Formula I and a variety of other selective T-channel antagonists as disclosed in claim 5.

The state of the art is relates to certain dihydropyrimidine, dihydropyrimidone, dihydropyrimidinethione, and dihydropyridine compounds that can modulate the activity of calcium channels. These compounds can also be used for the treatment of diseases, such as cardiovascular disease, that are associated with calcium channels.

The nature of the invention is drawn to a method of selectively inhibiting calcium T-channel activity with an array of active agents indicated to antagonize T-channel activity.

The presence of working examples in the specification is not sufficient in order to support the claims in this alleged invention. Specifically, applicants' attention is directed to Examples beginning at pages 40-71. Applicants' disclose in paragraph 143 [that] *the examples [...] are illustrative of some of the embodiments of the invention only and should not be construed to limit the scope of the claims.*

As a matter of initial importance with regard to applicants' preamble of paragraph 143, the embodiments that applicants' purport are represented in the said examples are deficient in as far as suggesting and/or adequately supporting a scope of invention drawn to the title Formula I and the variable compounds as disclosed in claim 5 for the selective inhibiting of T-channel activity.

The amount of direction and guidance disclosed in Examples 1-47 and Examples 48-50, respectively are deficient in as far as failing to show any reference of inhibition of T-cell activity with the title compound (Formula I) or any of the compounds as disclosed in said claim 5.

The explicit limitations claimed in claim 1 are no where represented throughout the examples. Examples 48-50 which are not drawn to synthesis of several of the compounds as disclosed in claim 5, do not resolve the deficiency in that the expression of T-type channels in Mammalian cells, Block studies, and Animal studies, respectively contain nothing in the way of being commensurate in scope with the limitations of claim 1 and 5.

In view of this invention, unpredictability would be high because the limitations of claim 1 which require a direct method of inhibiting calcium T-channel activity via the administration of Formula I and the compounds of claim 5 are absent with regard to any suitable explanation commensurate in scope with said claims 1 and 5.

Likewise, the quantity of experimentation necessary cannot be adequately determined. Example 1-50 lack any correlative data or cumulative results in order to clearly show a scope of a enablement for the method of administrations for claims 1 and 5 with the plethora of compounds as disclosed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY E. BETTON whose telephone number is (571)272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627